

Replace the paragraph beginning on page 10, line 7 with the following rewritten paragraph:

D2

-- As discussed herein, the blocking agents used in methods of the invention are not limited to antibodies or antibody derivatives, but may be other molecules, e.g., soluble forms of other proteins which bind VLA-4, e.g., the natural binding proteins for VLA-4. These binding agents include soluble VCAM-1 or VCAM-1 peptides, VCAM-1 fusion proteins, bifunctional VCAM-1/Ig fusion proteins, fibronectin, fibronectin having an alternatively spliced non-type III connecting segment, and fibronectin peptides containing the amino acid sequence EILDV (SEQ ID NO.:16) or a similar conservatively substituted amino acid sequence. These binding agents can act by competing with the cell-surface binding protein for VLA-4 or by otherwise altering VLA-4 function. For example, a soluble form of VCAM-1 (see, e.g., Osborn et al. 1989 [18]) or a fragment thereof may be administered to bind to VLA-4, and preferably compete for a VLA-4 binding site, thereby leading to effects similar to the administration of anti-VLA-4 antibodies. Soluble VCAM-1 fusion proteins can be used in the methods described herein. For example, VCAM-1, or a fragment thereof which is capable of binding to VLA-4 antigen on the surface of VLA-4 bearing cells, e.g., a fragment containing the two N-terminal domains of VCAM-1, can be fused to a second peptide, e.g., a peptide which increases the solubility or the *in vivo* life time of the VCAM-1 moiety. The second peptide can be a fragment of a soluble peptide, preferably a human peptide, more preferably a plasma protein, or a member of the immunoglobulin super family. In particularly preferred embodiments, the second peptide is IgG or a portion or fragment thereof, e.g., the human IgG1 heavy chain constant region. A particularly preferred fusion protein is the VCAM 2D-IgG fusion. --

Replace the paragraph beginning on page 10, line 35 with the following rewritten paragraph:

D3

-- In another aspect the invention features a chimeric molecule which includes: (1) a VLA-4 targeting moiety, e.g., a VCAM-1 moiety capable of binding to a VLA-4 antigen on the surface of VLA-4 bearing cells; (2) optionally, a second peptide, e.g., one which increases solubility or *in vivo* life time of the VLA-4 targeting moiety, e.g., a member of the immunoglobulin super family or fragment or portion thereof, e.g., a portion or a fragment of IgG,

D3 e.g., the human IgG1 heavy chain constant region, e.g., C_H2 and C_H3 hinge regions; and (3) a toxin moiety. The VLA-4 targeting moiety can be any naturally occurring VLA-4 ligand or fragment thereof, e.g., a VCAM-1 peptide, fibronectin, fibronectin having an alternatively spliced non-type III connecting segment, and fibronectin peptides containing the amino acid sequence EILDV (SEQ ID NO.:16) or a similar conservatively substituted amino acid sequence. A preferred targeting moiety is a soluble VCAM-1 fragment, e.g., the N-terminal domains 1 and 2 of the VCAM-1 molecule. The toxin moiety can be any agent which kills or inactivates a cell when the toxin is targeted to the cell by the VLA-4 targeting moiety. Toxin moieties include: cytotoxic peptide moieties, e.g., Diphtheria toxin A, *Pseudomonas* Exotoxin, Ricin A, Abrin A, *Shigella* toxin, or Gelonin; radionucleotides; and chemotherapeutic agents. --

Replace the paragraph beginning on page 12, line 2 with the following rewritten paragraph:

DA -- Experiments were performed essentially as described by Abraham et al. [8]. Briefly, allergic sheep having natural allergic cutaneous reaction to 1:1000 or 1:10,000 dilutions of *Ascaris suum* extract (Greer Diagnostics, Lenoir, N.C.) were tested, and sheep demonstrating both early and late phase airway response ("dual responders") to inhalation challenge with *Ascaris suum* antigen were selected. To measure breathing mechanics and physical changes in the airways, the sheep were restrained in a prone position with heads immobilized. A balloon catheter was advanced through one nostril under topical anesthesia with 2% lidocaine solution to the lower esophagus, and a cuffed endotracheal tube was advanced through the other nostril (using a flexible fiberoptic bronchoscope as a guide) for the measurement of airway mechanics and during aerosol challenges. Pleural pressure was estimated with the esophageal balloon catheter (filled with 1 ml of air) positioned 5-10 cm from the gastroesophageal junction. In this position, end expiratory pleural pressure ranged between -2 and -5 cm H₂O. Once the balloon was placed, it was secured so that it remained in position for the duration of the experiment. Lateral pressure in the trachea was measured with a sidehole catheter, (inner diam. 2.5 mm) advanced through and positioned distal to the tip of the endotracheal tube. Transpulmonary pressure (the difference between tracheal and pleural pressure) was measured with a differential pressure transducer catheter system (MP45, Validyne, Northridge, Calif.). The pressure

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transducer catheter system showed no phase shift between pressure and flow to a frequency of 9 Hz. Pulmonary resistance (R_L) was measured by connecting the proximal end of the endotracheal tube to a Fleisch pneumotachograph (Dyna Sciences, Blue Bell, Pa.). Signals indicating flow and transpulmonary pressure were recorded on an oscilloscope recorder (Model DR-12; Electronics for Medicine, White Plains, N.Y.) linked to a computer for automatic calculation of pulmonary resistance (R_L) from transpulmonary pressure, respiratory volume (obtained by digital integration) and flow by the mid-volume technique, analyzed from 5-10 breaths. Thoracic gas volume (V_{tg}) was measured immediately after determination of R_L in a constant volume body plethysmograph. Specific lung resistance (SR_L) was calculated from these values ($SR_L = V_{tg} \times R_L$). --

Replace the paragraph beginning on page 19, line 16 with the following rewritten paragraph:

D5
-- Wells of Immulon 2[®] plates (Dynatech, Chantilly, Va.) were each coated with anti-VCAM MAb 4B9 (isolated and purified on Protein A Sepharose as described by Carlos et al, 1990 :56!) with 100 .mu.l of anti-VCAM 4B9 MAb diluted to 10 µg/ml in 0.05M sodium carbonate/bicarbonate buffer, pH 9.6, covered with Parafilm[®] (thin sealing film), and incubated overnight at 4°C. The next day, the plate contents were dumped out and blocked with 200 µl/well of a block buffer (5% fetal calf serum in 1.times. PBS), which had been filtered through a 2 filter. The buffer was removed after a 1 hour incubation at room temperature and the plates were washed twice with a solution of 0.05% Tween-20 in 1XPBS. Conditioned medium was added at various dilutions. As a positive control, an anti-mouse Ig was also included. Block buffer and LFA-3TIP constituted as negative controls. The samples and controls were incubated at room temperature for 2 hours. --

Replace the paragraph beginning on page 20, line 9 with the following rewritten paragraph:

D6
-- CHO cells expressing VCAM 2D-IgG were grown in roller bottles on collagen beads. Conditioned medium (5 Liters) was concentrated to 500 ml using an Amicon[®] S1Y10 spiral ultrafiltration cartridge (Amicon, Danvers, Mass.). The concentrate was diluted with 1 liter of

D6 Pierce Protein A binding buffer (Pierce, Rockford, Ill.) and gravity loaded onto a 10 ml Protein A column (Sephacrose® 4 Fast Flow, Pharmacia, Piscataway, N.J.). The column was washed 9 times with 10 ml of Protein A binding buffer and then 7 times with 10 ml of PBS. VCAM 2D-IgG was eluted with twelve-5 ml steps containing 25 mM H₃PO₄ pH 2.8, 100 mM NaCl. The eluted samples were neutralized by adding 0.5M Na₂HPO₄ pH 8.6 to 25 mM. Fractions were analyzed for absorbance at 280 nm and by SDS-PAGE. The three peaks fractions of highest purity were pooled, filtered, aliquoted and stored at -70°C. By SDS-PAGE, the product was greater than 95% pure. The material contained less than 1 endotoxin unit per mg of protein. In some instances, it was necessary to further purify the Protein A eluate product on Q-Sephacrose® FF (Pharmacia). The protein A eluate was diluted with 3 volumes of 25 mM Tris HCl pH 8.0 and loaded onto a Q-Sephacrose® FF column at 10 mg VCAM 2D-IgG per ml of resin. The VCAM 2D-IgG was then eluted from the Q-Sephacrose® with PBS. --

In the claims:

For the Examiner's convenience, all of the pending claims have been reproduced below.

Please amend claims 1, 12, 13, and 26 as follows:

D7 -- 1. (Twice amended) A method for the treatment of allergic asthma comprising:
identifying a mammal suffering from allergic asthma; and
administering to the mammal a composition comprising a soluble fibronectin polypeptide.

----- 2. ----- (Reiterated) The method of Claim 1, wherein the composition is administered intravenously.

3. (Reiterated) The method of Claim 1, wherein the composition is administered in the form of an aerosol by inhalation.

6. (Reiterated) The method of Claim 1, wherein the composition is administered at a dosage so as to provide from 0.05 to 5.0 mg/kg of fibronectin polypeptide, based on the weight of the asthma sufferer.